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Engineered protein-like molecule protects cells against HIV infection

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(PhysOrg.com) -- With the help of the human immunodeficiency virus (HIV) and molecular engineering, researchers have designed synthetic protein-like mimics convincing enough to interrupt unwanted biological conversations between cells.

Interactions between proteins are fundamental to many biological processes, including some less-than-desirable ones like infections and tumor growth. For example, HIV and several other human viruses — including influenza, Ebola and the severe acute respiratory syndrome (SARS) virus — rely on interactions both among their own proteins and with host cell proteins to infect the cells.

"There's a lot of information transfer that occurs when proteins come together, and one would often like to block that information flow," says Samuel Gellman, a chemistry professor at the University of Wisconsin-Madison.

In a fundamental study of how to control protein shape, Gellman's UW-Madison research team, including former postdoctoral fellow W. Seth Horne, now at the University of Pittsburgh, and graduate student Lisa Johnson, created a set of peptide-like molecules that successfully blocked HIV infection of human cells in laboratory experiments.

By interacting with a piece of a crucial HIV protein called gp41, the synthetic molecules physically prevent the virus from infecting host cells.

The idea shows promise as a new avenue for targeting other unwanted protein interactions as well, Gellman says. The work, performed with a group led by John Moore and Min Lu at the Weill Medical College of Cornell University, is described in a paper appearing online this week (Aug. 17) in the Proceedings of the National Academy of Sciences.

Past attempts to prevent infection by selectively interfering with these interactions have had limited success, he says. Most drugs are small molecules and are not very effective at blocking most protein-protein interactions, which involve large molecular surfaces. Short snippets of proteins, or peptides, can be more effective than small molecules but are easily broken down by enzymes in the body and so require large and frequent doses that are difficult for patients to manage.

The new synthetic approach avoids these pitfalls by creating peptide-like molecules with a modified structure that degrading enzymes have trouble recognizing.

"We want to find an alternate language, an alternate way to express the information that the proteins express so that we can interfere with a conversation that one protein is having with another," Gellman explains.

Like engineers adjusting molecular blueprints, Gellman and his colleagues made structural tweaks to the backbones of their synthetic molecules to improve stability while retaining the three-dimensional shape necessary to recognize and interact with the HIV gp41 protein. The resulting molecules — dubbed "foldamers" — are hybrids of natural and unnatural amino acid building blocks, a combination that allows the scientists to control shape, structure and stability with much greater precision than is currently possible with natural amino acids alone.

In addition to adopting a shape that can interrupt the protein-protein dialogue, the novel foldamer has the additional advantage of being

highly resistant to degradation by naturally occurring enzymes, which are stymied by the foldamer's unusual structure. This means the molecule can remain effective for a longer time and at lower doses.

Several of the synthetic foldamers showed potent antiviral activity against HIV when applied to cultured human cell lines in a dish. Although it is not clear that the foldamers themselves could ever be used as anti-HIV drugs, Gellman emphasizes, the results show that this type of approach has great potential to lead to new ways to think about designing molecules for antiviral therapies and other biomedical applications.

"You don't have to limit yourself to the building blocks that nature uses," Gellman says. "There's a huge potential here because the strategy we use is different from what the pharmaceutical and biotech industries now employ."

Source: University of Wisconsin-Madison (news : web)